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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,249	11/03/2004	Kazuyoshi Yajima	5404/79	8933

7590 02/08/2007

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EXAMINER	
AFREMOVA, VERA	
ART UNIT	PAPER NUMBER
1657	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,249	YAJIMA ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,16,18-21,24,29-31,58-60,65-73,75 and 76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,16,18-21,24,29-31,58-60,65-73,75 and 76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/13/2006 has been entered.

Claims 1, 4, 5, 16, 18-21, 24, 29-31, 58-60, 65-73, 75 and 76 as amended (11/13/2006) are under examination in the instant office action.

No new claims were submitted on 11/13/2006. Claim 58 is erroneously identified as "new" claim in the amendment filed on 11/13/2006.

Claims 2, 3, 6-15,17, 22, 23, 25-28, 32-57, 61-64 and 74 were canceled by applicants.

Applicant's election without traverse of a single species such as *Rhodobacter* (claim 31) in the reply filed on 8/15/2005 was acknowledged in the prior office action(s).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 5, 16, 18-21, 24, 29-31, 58-60, 65-73, 75 and 76 as amended remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 3,769,170 (Kondo et al.) and Yoshida et

al. (IDS reference A33; J. Gen. Appl. Microbiol. 1988, 44:19-26) taken with US 6,156,802 (Mae et al.), Venturoli et al. (Biochimica et Biophysica Acta, 935 (1988) 258-272) and Wakabayashi et al. (Biol. Pharm. Bull. 1994, 17(8): 997-1002).

Claims are directed to a process for producing reduced coenzyme Q10 wherein the method comprises step of culturing the reduced coenzyme Q10-producing microorganisms in a culture medium, step of disrupting the cells and extracting thus-produced reduced coenzyme Q10 by an organic solvent and under conditions that prevents oxidation of Q10 during disrupting/extracting steps. Some claims are further drawn to the culturing step culture conditions including temperature 15-45 degree C, pH of 4 to 9, aerobic cultivation, fed batch cultivation. Some claims are further drawn to the disrupting cells by physical treatment including heating, homogenizers and/or beads. Some claims are further drawn to the extracting step comprising the use of organic solvent(s) including hydrophilic solvents such as acetone, methanol, ethanol, propanol and hydrophobic solvents including hexane. Some claims are further drawn to analyzing the Q10 by HLPC. Some claims are further drawn to purifying and crystallizing Q10.

The cited documents US 3,769,170 (Kondo et al.) and Yoshida et al. are relied upon for the disclosure of methods for producing coenzyme Q10 including reduced Q10 by various microorganisms including the elected species of *Rhodobacter sp.* (Yoshida et al.) wherein the methods of the cited documents comprise steps of culturing cells, disrupting cultured cells, extracting Q10 and purifying Q10.

For example: US 3,769,170 (Kondo et al.) discloses a process for producing reduced coenzyme Q10 (entire document) wherein the method comprises step of culturing the reduced

coenzyme Q10-producing microorganisms in a culture medium containing a carbon source, a nitrogen source a phosphorous source and a micronutrient (for example: see at col. 2, lines 5-17) at temperature 20-37 degree C, at pH of 2 to 8, under aerobic cultivation and by fed batch cultivation (col. 2, lines 18-24). The cited patent teaches step of obtaining cells and disrupting cells by heating (col. 2, lines 30). The cited patent teaches step of extracting by using organic solvents including hydrophilic solvents such as acetone, methanol, ethanol, and hydrophobic solvents including hexane (col. 2, line 31-35; col. 3, lines 1-10). Hexane is used as sole solvent at least during some extraction/separation steps, and, thus, the extraction is carried out under about neutral conditions. The cited patent teaches step of purifying and crystallizing Q10 (col. 2, line 35; col. 3, lines 10-14). The microbial cells disclosed by US 3,769,170 produce coenzyme Q10 in outstanding amounts, for example: tables 1-3 demonstrate Q10 amounts calculated in mg/g of dried cells. The cited microorganisms include species and particular strains that are identical to the applicants' cultures, for example: *Candida curvata* ATCC 10567 (examples 4 and 5) and *Cryptococcus laurentii* IFO 609 (table 1). For comparison see instant specification at table 1. The culture conditions are identical as claimed and as disclosed. Thus, the claimed amounts of reduced Q10 that are calculated as mg/ml and as ratio not less than 70 mole % are inherently identical since the same microorganisms are cultured under the same conditions. Moreover, that the process of the example 4 (col. 4, lines 55-67) appear to result in the production of about 6 μg/ml of coenzyme Q10 (370μg x 78g/5000ml).

For example: Yoshida et al. discloses a process for producing coenzyme Q10 by *Rhodobacter sp.* (table 1, last line) wherein the method comprises step of culturing *Rhodobacter sp.* in a culture medium containing a carbon source, a nitrogen source a phosphorous source and

a micronutrient (page 20, column 1, par. 1), obtaining microbial cells and extracting coenzyme Q10 (page 20, column 1, last par.). Coenzyme Q10 is analyzed by HPLC. The cited reference teaches cell disruption with beads and the use of propanol-hexane mixture as extracting solvent. The culture conditions include temperature 30 degree C, pH of about 7, aerobic cultivation and fed batch cultivation (page 20, col. 1) including fed-batch addition of carbon source separately from other components (page 20, col.1, par.1, last line). The cited reference discloses culturing the same microorganism (the elected species of *Rhodobacter* of claim 31) under the same conditions as required by the claimed method and thus, the amounts of produced Q10 are identical as claimed. Moreover, the table 1 demonstrates that *Rhodobacter* produces about 95 mg/L of coenzyme Q10.

Thus, the microorganisms including *Rhodobacter sp.* and the culturing conditions in the methods of US 3,769,170 (Kondo et al.) and of the reference by Yoshida et al. are identical to the presently claimed microorganisms and to the presently claimed culturing conditions.

US 3,769,170 teaches cell disruption by heating and the use of several solvents including hexane for extracting Q10. Yoshida et al. teaches cell disruption with beads and the use of propanol-hexane mixture for extracting Q10 (page 20, col.1, last par.).

US 3,769,170 teaches purification of Q10 on silica column and analyzing Q10 by paper chromatography. The reference by Yoshida et al. teaches analyzing and measuring Q10 by HLPC.

Thus, the cited references teach the same active steps as encompassed by the presently claimed method. In the methods of the cited references the coenzyme Q10 is extracted as a total

pool. Thus, the references appear to lack particular considerations with regard to conditions preventing oxidation-reduction of coenzyme Q10 during disruption/extraction step(s).

However, US 6,156,802 (Mae et al.) teaches that the coenzyme Q10 is involved in electron transport in living cells from microorganisms to higher animals and both forms are readily transformed into each other in the living cells *in vivo* (see US 6,156,802 at col. 3, lines 45-65). Further, the reference by Venturoli teaches that precise measurement related to electron transfer or electrogenic reactions are performed in nitrogen atmosphere and under controlled red-ox conditions including applications involving extracts from *Rhodobacter sp.*

The methods of simultaneous determination of oxidized and reduced forms of Q10 in biological samples are known as taught by Wakabayashi et al.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to control the red ox conditions and/or to use "reduction" conditions including deoxygenized atmosphere during disruption/extraction of cells containing coenzyme Q with a reasonable expectation of success in preventing oxidation of the reduced form of Q10 and obtaining, measuring or analyzing the reduced form of coenzyme Q10. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary. One of skill in the art would have been motivated to obtain the reduced form of Q10 because the reduced Q10 is a therapeutically valuable antioxidant.

With respect to claim 29 it is noted that the reference by Yoshida et al. teaches substantially the same, if not identical, conditions including same nutrients, the use of test tube of the similar size, similar speed of rotary shaker, etc. for culturing the elected species of *Rhodobacter*.

Therefore, the claimed subject matter fails to patentably distinguish over the state art as represented be the cited references, especially in the absence of evidence to the contrary. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicants' arguments filed 11/13/2006 have been fully considered but they are not persuasive.

Applicants' arguments are directed to the idea the cited references US 3,769,170 (Kondo et al.) and Yoshida et al. (J. Gen. Appl. Microbiol. 1988, 44:19-26) do not discloses steps of cell disruption and extraction of Q10 under conditions that the reduced Q10 is protected from oxidation (response page 8). Applicant also argue that the cited prior art references including US 3,769,170 (Kondo et al.) and Yoshida et al. do not recognize the presence of reduced form of coenzyme Q in microorganisms (response page 9).

These arguments do not have persuasive grounds because the prior art including the cited US 3,769,170 (Kondo et al.) in particular, refers to coenzyme Q as an entire coenzyme Q including both ubiquinone (oxidized) and ubiqionol (reduced) forms. The reference by Yoshida et al. discloses quantification of entire coenzyme Q as ubiquinone. Most importantly and as related to the presently claimed invention, the cited references teach production of coenzyme Q by the same microorganisms as the claimed microorganisms. For example: US 3,769,170 (Kondo et al.) teaches production of coenzyme Q by identical species and even by identical strains, for example: *Candida curvata* ATCC 10567 (examples 4 and 5) and *Cryptococcus laurentii* IFO 609 (table 1), as the applicants microbial species and particular strains, for

example: see instant specification table 1. The culture conditions are identical as claimed (claim 1) and as disclosed by the prior art. Thus, the prior art teaches obtaining microbial cells and/or some crude microbial cell extract that inherently contain not less than 70 mole % of reduced coenzyme Q.

The presently claimed culture conditions and the extraction conditions are generic and ambiguous, for example: claims 1 and 74. The claimed culture conditions and the extraction do not identify any specific parameters that would distinguish them from the prior art methods conditions. Moreover, regardless special precautions during extraction of coenzyme Q from microbial cells as it might be intended, exposure of the extracted coenzyme Q to air would result in total oxidation of coenzyme Q (see specification page 32, line 25).

Therefore, the Applicants' arguments amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the prior art.

It is well know that the coenzyme Q10 is involved in electron transport in living cells from microorganisms to higher animals and both forms are readily transformed into each other in the living cells (see US 6,156,802 at col. 3, lines 45-65). Thus, the crude microbial cell extract would inherently contain reduced forms of coenzyme. The methods of simultaneous determination of oxidized and reduced forms of Q10 in biological samples are known as taught by Wakabayashi et al.

With regard to the cited references by Wakabayashi et al. and by Venturoli et al. applicants appear to argue that the references relate to animal organisms but not to microbial

cells. However, the references are relied upon as related to separation and quantification of coenzyme Q and, thus, its source is irrelevant.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1657

February 2, 2007

VERA AFREMOVA

PRIMARY EXAMINER